**Evaluation of Transdermal Absorption of Ketoprofen in a Rabbit Model**

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**Materials & Methods (continued)**

Ketoprofen, R,S-2-(3-Benzoylphenyl) propionic acid, is a traditional non-steroidal anti-inflammatory drug (NSAID) commonly administered orally as an anti-inflammatory agent, analgesic, and anti-pyretic. It exerts its action by inhibiting the COX-1 and COX-2 enzymes which mediate the formation of prostaglandin precursors and thus controls pain, inflammation, and fever in the body[1,2]. As an oral preparation, absorption of ketoprofen is almost complete, making this type of therapy very effective[3]. A known adverse effect of this administration route, however, is gastrointestinal irritation and ulceration due to the local effects of prostaglandin synthesis suppression in the gastric mucosa as the drug undergoes absorption[4]. Also, a number of patients are not good candidates for oral therapy due to age, disease state, or other factors.

A potential drug delivery system that would overcome these problems is a topical preparation such as a gel. Based on the physiochemical and pharmacokinetic properties of this NSAID, transdermal absorption of ketoprofen is possible[5]. The primary purpose of this study was to assess the extent to which this drug can be absorbed transdermally from a gel preparation and to analyze whether therapeutic drug levels can be achieved to provide systemic anti-pyretic. It was possible that the plasma levels of ketoprofen were not significantly higher than those of the blank baseline indicate that significant systemic absorption of ketoprofen from a transdermal gel preparation could not be detected. Additionally, the trace levels observed were transient and variable. This finding suggests further studies are needed to evaluate higher doses of compounded ketoprofen transdermal gels. The results of this study also bring into question the usefulness of a rabbit model to test potential transdermal absorption of ketoprofen in vivo due to significant metabolic and physiological differences from a human model. Future studies should consider a different assay to detect ketoprofen plasma levels.

**Disclosure Statement**

The authors of this presentation have the following to disclose concerning possible financial or personal relationships with the commercial entities that may have direct or indirect interest in the subject matter of this presentation:

Arthur H. Kibbe: Nothing to disclose

Adam L. VanWert: Nothing to disclose

Eliza S. Daubert: Nothing to disclose

Christina Inteso: Nothing to disclose

Manuel Isherwood: Nothing to disclose

Trey Tietz: Nothing to disclose

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**Materials & Methods**

Ketoprofen and all other materials needed to compound the gel formulations were purchased from Sigma-Aldrich. Lipoderm base was purchased from the Professional Compounding Centers of America (PCCA). Ammonium sulfate was obtained from Acros Organics. HPLC grade acetonitrile was purchased from Spectrum. Xylenes and HPLC grade methanol were procured from Fisher Scientific. Four New Zealand white rabbits approximately 1.5 kg each were obtained from Charles River Laboratories.

The Water’s HPLC system included a 717 plus autosampler, a 600 solvent delivery pump, a 486 tunable absorbance detector, and a Supelco 18-LC analytical column. The chromatographic separation was performed through injection of 20 μL samples at room temperature (22 °C) and detected at 265 nm. The mobile phase consisted of 59% methanol, 26% acetonitrile, and 15% water.

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**Results**

A standard curve of ketoprofen gave linear results with a correlation coefficient of 0.999 and a retention time of 5 minutes. Unfortunately, due to a confounding endogenous substance in the rabbit plasma, minimal baseline separation was observed. The Lipoderm® gel showed slightly higher peaks in comparison to the PLO gel formulation. The results for the four rabbits, each treated with the same dose of ketoprofen in two different vehicles, appear in Figure 2, to right.

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**Discussion/Conclusions**

The results showing peaks of the ketoprofen plasma samples were not significantly higher than those of the blank baseline indicate that significant systemic absorption of ketoprofen from a transdermal gel preparation could not be detected. Additionally, the trace levels observed were transient and variable. This finding suggests further studies are needed to evaluate higher doses of compounded ketoprofen transdermal gels. The results of this study also bring into question the usefulness of a rabbit model to test potential transdermal absorption of ketoprofen in vivo due to significant metabolic and physiological differences from a human model. Future studies should consider a different assay to detect ketoprofen plasma levels.

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**References**


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**Materials & Methods (continued)**

The mobile phase was delivered at a rate of 1.2 mL/min and time between injections was 10 minutes[6]. Solutions of 0.5 μg/μL, 5 μg/μL, 10 μg/μL, 100 μg/μL and 1 mg/μL ketoprofen in acetonitrile were prepared and used to construct a standard curve.

Ketoprofen was formulated into two commonly used transderal preparations as shown in Figure 1, below:

The first formulation used Pluronic-Lecithin-Organogel (PLO) as a base[6].

The organic phase, composed of Lecithin, was made by the general formula below:

Preparation of Lecithin Solution

Lecithin Soybean Granular

100 gm

Sorb,Acid NF

660 mg

Isopropyl Palmitate

100 gm

The aqueous phase, composed of a Pluronic 127 gel, was made using the following formula:

Preparation of Pluronic 127 NF 20% Solution

Pluronic 127 NF

20 gm

Potassium Sorbate

300 mg

Distilled Water

100 mL QS

The ketoprofen was dissolved in the lecithin solution before introducing the aqueous Pluronic phase then mixed well to form a homogenous gel.

The second formulation used PCCA’s Lipoderm® base. The gel was made based on the following formula:

Preparation of 1% Ketoprofen Lipoderm TDG

Ketoprofen USP

30 mg

PCCA Lipoderm®

3 mL QS

Propylene glycol

2 gts

Ketoprofen was dissolved in propylene glycol and mixed well with the Lipoderm® base.

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**Figure 1: Ketoprofen Gel Formulations**

The Institutional Animal Care and Use Committee (IACUC) approved the study protocol. The four rabbits were housed in a normal 12 hour light/dark environment with water freely available and were fed 150 grams of standard rabbit chow daily in addition to grass. To carry out this study, a given animal was restrained in a rabbit stock and the inside of one ear was dosed with 0.2 mL of 1 percent ketoprofen gel (1 mg/kg). Blood was collected in heparinized tubes from the marginal veins of the opposite ear at time intervals of 0, 0.5, 1, 1.5, and 2 hours. The plasma was separated via centrifugation at 2000 g for 2 minutes and stored at 5 °C for further analysis.

The extraction procedure utilized a sample of 100 μL of plasma to which 400 μL acetonitrile was added[6]. This was vortex mixed for 2 minutes and centrifuged at 21000 g for 5 minutes. The clear supernatant was utilized for HPLC analysis. After establishing a steady baseline, the standard and plasma samples were injected and the resulting chromatogram recorded. Linear regression of the standard curve data was calculated by plotting the peak area against the drug concentration in micrograms per millimeter.

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**Figure 2: Ketoprofen Levels in Rabbits**

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